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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,8,10-17,22,24 and 29-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8,10-17,22,24 and 29-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 4/22/2005 is acknowledged. Claims 1,2,4,8,10-17, 22, 24 and 29-43 are pending in the instant application. Applicant canceled claims 3,5-7,9, and amended claims 1,12 and 22 and 42, and added claims 29-43. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

The rejection of claims 1-7 and 12-15, 17, and 22 under 35 U.S.C. 102(b) as being anticipated by Jaleco et al. {Jaleco et al. (2001) J. Exp. Med. 194:991-1001}, is withdrawn in view of applicants amendments to the claims.

Claim Rejections - 35 USC § 112

Claims 1,2,4,8,10-17, 22, 24 and 29-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* system comprising OP9 stromal cells that express Delta-like 1 ligand, that supports αβ CD4+ CD8+ T cells, αβ CD4- CD8+ T cells and γδ T cell lymphopoiesis from hematopoietic progenitor cells, hematopoietic stems cells and mouse embryonic stem cells, but does not support B cell lymphopoiesis, does not reasonably provide enablement for an *in vitro* system comprising any stromal cells expressing any Notch ligand that supports any and all T cell lymphopoiesis from any cell but does not support B cell lymphopoiesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The rejection of claims 3,5-7,9 is withdrawn due to their cancellation.

Claims 29-43 are newly rejected. This new rejection was necessitated by applicant's addition of the claims.

Response to Arguments

Applicant's arguments filed 4/22/2005 have been fully considered but they are not persuasive. The previous office action identified the following issues of record: **1)** failure to provide guidance on the use of any stromal cells other than OP9 ; **2)** failure to provide guidance on the use of any other Notch ligands other than Delta-like 1; **3)** lack of an enabling disclosure for the development of all T cell lineages; **4)** lack of guidance that any T cell can be developed from any starting cell.

1) Applicant's have amended claim 1 to read only on OP9 stromal cells. Therefore this rejection no longer applies to claims 1,2,4,8,10-17, 22, and 24. However, applicant has added claims 29-43 which are drawn to a method using murine stromal cell to support murine T cell lymphopoiesis. Applicant suggests that Example 9 provides enablement for these claims. This is not found to be persuasive. Applicant states in example 9 that the S-17 cells must be transfected with Delta-1 in order to not support B cell lymphopoiesis. The specification does not provide any guidance on the transfection of S-17 cells, and this element is left out of all the claims of 29-43. Further the claims broadly read on any mouse stromal cell, Mouse stromal cells other than OP9 may lack important factors and/or express negative modulators of Notch receptor or Notch ligand function, such as Fringe or Neutralized (Specification pg. 49, lines 25-30). Given the, the teachings in the specification on the problems associated with using S17 in the claimed method

and the total lack of evidence disclosed that S17 cells can be used in the claimed method to induce T lymphopoiesis in murine cells, the rejection over this issue is maintained over new claims 29-43 for reasons of record as set forth in the office action of 1/25/2005.

2) Applicant has amended the claims to specify that the stromal cells must express DL-1. However the have also added that in the alternative the cells may express DL-4 and suggest that support for this may be found in examples 1 and 3 of the specification. First, it is noted that the specification teaches that the wild-type OP9 cells do not express DL-1 or DL-4 (Specification pg. 31, lines 20-25). Since the method of claims 1,2,4,8,10-17, 22, 24 requires that DL-1 or DL-4 be expressed in the OP9 cells the method claims should contain a positive step indicating that the OP9 cells have been transfected with expression vectors containing the relevant sequences. However, Examples 1 and 3 provide enablement for OP9 cells expressing DL-4. The rejection over this issue is withdrawn in view of applicant's amendments to the claims and arguments.

3) Applicant argues that one of skill in the art could readily determine how to modify the system in order to produce αβ CD4+ CD8- T cells. Further applicant cites Rothenburg and Lehar, provided by the examiner in the previous action, to support their contention that one of skill in the art would readily know to include MHC class II molecules to produce αβ CD4+ CD8- T cells. Finally, they argue that any experimentation would not be undue but would merely be adapting the invention. This is not considered persuasive. Applicant has not demonstrated in the specification that expression of MHC class II molecules on OP9 cells is sufficient to induce cells in their system. Further, the specification does not indicate that applicant even contemplated

transfecting the OP9 cells with MHC II expression vectors as a step in their claimed method. Based on the guidance provided in the specification and the lack of teachings in the art at the time of filing on how to induce lymphopoiesis of any mature T cell the skilled practitioner would not have been able to predict how to practice the claimed invention in a manner commensurate with the full breadth of the claims. The rejection over this issue is maintained over the claims for reasons of record as set forth in the office action of 1/25/2005.

4) Applicant's amendments to the claims and arguments presented are found to be persuasive. The rejection over this issue is withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,2,4,8,10-17, 22, 24 and 29-43 are newly rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: The transfection of OP-9 or the mouse stromal cell with a vector encoding DL-1 or DL-4. The specification discloses that OP-9 cells or S-17 stromal cells must be transfected with DL-1 or DL-4 in order to induce T cell lymphopoiesis but not induce B cell lymphopoiesis (Specification pg. 31, lines 20-25; pg. 49, lines 5-10). This new rejection is necessitated by applicant's amendments to the claims, and addition of new claims.

Double Patenting

The rejection is withdrawn in view of applicant's arguments.

Claim Rejections - 35 USC § 102

The rejection of claims 1-7 and 12-15, 17, and 22 under 35 U.S.C. 102(b) as being anticipated by Jaleco et al. {Jaleco et al. (2001) J. Exp. Med. 194:991-1001}, is withdrawn in view of applicants amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2,4,8 and 12-15, 17, 22, 29-33,36-39, 41-42 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al. {Jaleco et al. (2001) J. Exp. Med. 194:991-1001}, in view of Nakano et al. {Nakano et al. (1994) Science 265:5175} and Tatsumi et al. {Tatsumi et al. (1990) Proc. Natl. Acad. Sci. 87:2750-2754}. This new rejection is necessitated by applicant's amendments to the claims, and addition of new claims.

Jaleco et al. provides guidance on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of human hematopoietic progenitor cells (HPCs) but does not support B cell lymphopoiesis (Abstract). Specifically, Jaleco et al. teaches that culturing HPCs with mouse S-17 stromal cells that express Delta-1 inhibits B cell differentiation and

produces CD3+ CD4+CD8+ T cells (pg. 992, Materials and Methods; pg. 995, Table 1). Abbas et al. teaches that T cells that are CD3+ CD4+CD8+ have inherently undergone TCR V(D)J rearrangement {Abbas et al., (1994) Cellular and Molecular Immunology 2nd ed., 1-457; pg. 176, Fig. 8-5; pg.178 col. 1}. Jaleco et al. teaches that transfecting S-17 stromal cells specifically blocks B cell lymphopoiesis (Abstract). Further, Jaleco et al. teaches that the immature T cells were separated from the aggregate population of cells (pg. 995, Table 1). Jaleco et al. does not teach using OP-9 stromal cells or inducing lymphopoiesis in mouse cells.

Nakano et al. supplements the guidance of Jaleco et al. by teaching the use of mouse OP-9 stromal cells (which inherently does not express M-CSF) to generate lymphohematopoietic cells (Abstract). Nakano et al. teaches that it is advantageous to use stromal cells lacking M-CSF when studying lymphopoiesis because the presence of M-CSF can inhibit the differentiation of ES cells to blood cells other than macrophages.

Tatsumi et al supplements the guidance of Jaleco et al. by teaching an *in vitro* system for studying the differentiation of mature mouse T cells from CD3- CD4-CD8- precursors by culturing them with mouse stromal cells (Abstract; pg. 2750, Materials and Methods).

Based on the guidance provided by Jaleco et al. on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of HPCs but does not support B cell lymphopoiesis and the teachings of Nakano et al. on the advantages of using OP-9 cells when studying lymphopoiesis, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Jaleco et al. by replacing the mouse S-17 stromal cells with OP-9 cells. Further it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the assay system of

Jaleco et al. with the OP-9 cells of Nakano et al. to study mouse T cell differentiation with the mouse precursor cells using the precursors taught by Tatsumi et al.

A practitioner in the art would be motivated to modify the method of Jaleco et al. with the OP-9 cells of Nakano et al. in order to reduce the number of inhibitory ligands and to optimize T cell induction. Further the practitioner would be motivated to use this system to study mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced

The person of ordinary skill in the art would have a reasonable expectation of success because the modifying the teachings of Jaleco et al. by replacing the S-17 stromal cells with the OP-9 cells of Nakano et al. would have been a routine modification in the art at the time of filing. Further, the use of mouse hematopoietic precursor cells, such as those taught by Tatsumi et al. , instead of human hematopoietic precursors would have been a routine modification in the art at the time of filing.

No claims allowed

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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